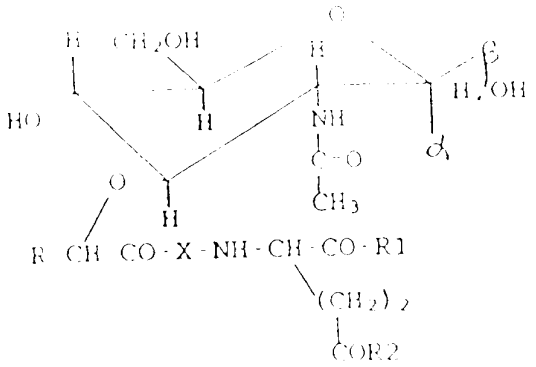
the present invention relates to a process for inhibiting the replications of acquired immunodeficiency retroviruses by administering as an active ingredient an effective amount of a muramyl peptide of the formula:



in which the group R is a methyl group; X is an L-alanyl residue, and R1 is an $O(CH_2)_xH$ group with x= 1, 2, 3 or 4, R2 is, independently of R1, either an amino or an $O(CH_2)_xH$ group with x= 1, 2, 3 or 4, wherein said effective amount is also an amount that is capable of causing a 100% inhibition of the replication of the retrovirus in the primary cultures of monocytes of the host.

It should be brought to the immediate attention of the Examiner that by definition, an adjuvant is an ingredient (as in a prescription or a solution) that modifies the action of the principal ingredient (see, enclosed Annex I).

Applicant submits that the presently claimed invention distinguishes the presently claimed invention over the cited prior art of record since the muramyl peptide is in fact the principal ingredient which is administered, as now set forth in the claims and hence is not acting as an adjuvant.

Turning now to the Official Action, Claims 14 to 24 have been canceled to solely to expedite the prosecution of the present application and not to acquiesce to any of the Examiner's rejections, including the prior art rejections. Applicant reserves their right to file a continuing prosecution application directed to the canceled subject matter. Claims 22, 29, 31 and 34 have been amended solely to clarify the present invention. Claims 35 to 40 have been added. Support for Claim 37 appears at least

on page 7, last full sentence of the application as filed. Support for the term principal ingredient appears at least in the paragraph bridging pages 6 and 7 of the specification. Applicant submits that no new matter has been added via this amendment.

Claims 22 and 31 have been rejected under 35 U.S.C. § 112, second paragraph. Claim 22 has been canceled. Claim 31 has been amended to delete "such as", which should render this rejection now moot.

Claims 14 to 21, 25, 26, 28 to 30 and 34 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Schreck et al. As far as this rejection may pertain to the Claims currently of record, it is respectfully traversed.

Schreck et al teach the use of muramyl peptides as **adjuvants** in potential vaccines against AIDS. Schreck et al disclose that it would be beneficial to select **adjuvants** that do not induce NF-κB activation and particularly if the vaccines are to be aimed at treating seropositive individuals. More specifically as stated at page 188 of this publication and in the Summary out of all the muramyl peptides tested, **only one** new lipophilic nonpyrogenic adjuvant muramyl peptide (MDP) (thr-glyceryl-dipalmitoyl (MDP (thr)-GDP) demonstrated the lack of NF-κB activation in all cell lines tested. More specifically, the following is stated at page 188:

> Our results demonstrate a lack of NF-κB activation in all cell lines tested, by **one** new lipophilic, nonpyrogenic, adjuvant active muramyl peptide MDP (thr)-glyceryl-dipalmitoyl (MDP (thr)-GDP). **In contrast, all other immunostimulants examined induced activation of NF-κB in one or more cell lines.** Furthermore, we present evidence that stimulation of one or more cell lines with MDP (thr)-GDP results in productive interaction with the cells as manifested by the induction of IL-8 gene expression. The novel MDP derivative may therefore be the **adjuvant** of choice to be incorporated into AIDS vaccines (emphasis added).

Thus, Schreck et al do not lead the skilled artisan to choose murabutide as an adjuvant for an AIDS vaccine since it does not demonstrate a lack of NF-κB

activation in all cell lines tested. Indeed, as stated at page 190, activation of NF-κB was noted in the human Mono-Mac-6 cell line following stimulation with 10 μg/ml of murabutide. Therefore, Schreck et al encourage the use of only MDP (thr)-GDP only as an adjuvant and not murabutide.

Moreover Schreck et al **do not disclose that murabutide can be used in a process for inhibiting the replication of HIV**. Rather Schreck et al describe the use of murabutide as an adjuvant in an AIDS vaccine, the "primary ingredient" in the vaccine is not disclosed, to enhance specific immune responses against the virus.

As discussed above, an adjuvant is an ingredient (as in a prescription or a solution) that modifies the action of the principal ingredient. An adjuvant is not the principal ingredient in a vaccine, as the skilled artisan well knows.

Thus, Schreck et al do not disclose murabutide of itself to inhibit HIV and the effect of murabutide on virus replication in the present invention is not mediated by its adjuvant effect and enhancement of specific immunity to HIV but through nonspecific mechanisms since monocytes/macrophages do not exert antigen-specific immune responses which are totally restricted to lymphocytes.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 14 to 21, 25, 26, 28 to 30 and 34 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Masihi et al. As far as this rejection may pertain to the Claims currently of record, it is respectfully traversed.

Masihi et al disclose that muramyl dipeptide can enhance monocyte-macrophage CSF in serum and promote nonspecific resistance against a variety of microbial pathogens including HIV infection of $CD4^+$ H9 lymphocytes and U937 monocytoid cells, which are not primary cultures of monocytes.

At page 397 murabutide was taught to be used as an adjuvant in human clinical trials. The Examiner purports that Masihi et al teach that murabutide can be used as an adjuvant in "human clinical trials for AIDS." However, this reference does not state this. Rather, Masihi et al strictly teach that murabutide can be used as an **adjuvant** in human clinical trials; the specific clinical trials are not disclosed and the ability of murabutide to completely inhibit HIV replication in primary culture cells has never been eluded to.

Moreover, as discussed above, an adjuvant is solely used as a vehicle to modify the action of the principal ingredient. Thus, Masihi et al fail to teach that murabutide can be used as the principal ingredient in a process to treat AIDS directly. Therefore, this reference fails to anticipate the presently claimed invention.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

Claims 14 to 21, 25, 26, 28 to 30 and 34 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over by Masihi et al. As far as this rejection may pertain to the Claims currently of record, it is respectfully traversed.

As discussed above, Masihi et al fail to teach the skilled artisan that murabutide can be used in a process as the principal ingredient for inhibiting the replication of HIV. Rather, murabutide was taught to be used only as an adjuvant in human clinical trials.

Furthermore, Masihi et al teach the antiviral activity of MDP, not murabutide to include HIV infection. The Examiner relies on a sole sentence in this reference to incorrectly render the present rejection. Applicant submits that this reliance could be made solely through hindsight reproduction which is not the appropriate standard to render an obviousness rejection.

Moreover, Masihi et al. disclose only 67% reduction of the p24 antigen using MDP and only a 38% inhibition on day 14 using infected CD4* KE37/I lymphocytes and further teach that 1000 μg/ml dosages were more effective. This is an extremely high dosage and the side effects of MDP to the recipient would be enormous at this particular dosage, which fact is discussed in the background of the present invention. In contrast, new Claim 37 recites that the dosage to be administered is between 1 and 500 μg/kg/day.

Moreover, the present invention teaches 100% inhibition of the AIDS retrovirus in primary cultures of monocytes. Therefore, this is an unexpected result that his not taught in the prior art.

Thus, in view of the above, withdrawal of this rejection is respectfully requested.

As the above-presented amendments and remarks address and overcome the rejections of the Examiner, withdrawal of the rejections and reconsideration and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Should the Examiner have any questions regarding the present application, he is requested to contact Leonard R. Svensson at (714) 708-8555.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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LRS/MAL/cpw
Attachment

ANNEX I

ad·junct [illegible] *n* [L *adjunctum*, neut. of *adjunctus*, pp. of *adjungere*] [illegible] **1** : something joined or added to another thing but not essentially a part of it **2** : a word or word group that qualifies or completes the meaning of another word or other words and is not itself a main structural element in its sentence **3** : an associate or assistant of another — **ad·junc·tive** \[illegible]\ *adj*

²**adjunct** *adj* (1595) **1** : added or joined as an accompanying object or circumstance **2** : attached in a subordinate or temporary capacity to a staff (an ~ psychiatrist) — **ad·junct·ly** \[illegible]\ *adv*

ad·junc·tion \[illegible]\ *n* (1618) : the act or process of adjoining

ad·ju·ra·tion \[illegible]\ *n* (1611) **1** : a solemn oath **2** : an earnest urging or advising — **ad·jur·a·to·ry** \[illegible]\ *adj*

ad·jure \[illegible]\ *vt* **ad·jured**; **ad·jur·ing** [ME *adjuren*, fr. MF & L; MF *ajurer*, fr. L *adjurare*, fr. *ad-* + *jurare* to swear — more at JURY] (14c) **1** : to command solemnly under or as if under oath or penalty of a curse **2** : to urge or advise earnestly *syn* see BEG

ad·just \ə-ˈjəst\ *vb* [MF *ajuster*, fr. MF *ajuster* to gauge, adjust, fr. *a-* (fr. L *ad-*) + *juste* right, exact — more at JUST] *vt* (14c) **1 a** : to bring to a more satisfactory state (1) : SETTLE, RESOLVE (2) : RECTIFY **b** : to make correspondent or conformable : ADAPT **c** : to bring the parts of to a true or more effective relative position (~ a carburetor) **2** : to reduce to a system : REGULATE **3** : to determine the amount to be paid under an insurance policy in settlement of (a loss) ~ *vi* **1** : to adapt or conform oneself (as to climate, food, or new working hours) **2** : to achieve mental and behavioral balance between one's own needs and the demands of others *syn* see ADAPT — **ad·just·abil·i·ty** \-ˌjəs-tə-ˈbil-ət-ē\ *n* — **ad·just·able** \-ˈjəs-tə-bəl\ *adj* — **ad·jus·tive** \-ˈjəs-tiv\ *adj*

ad·just·ed *adj* (1674) **1** : accommodated to suit a particular set of circumstances or requirements **2** : having achieved a harmonious relationship with the environment or with other individuals (a well-*adjusted* schoolchild)

ad·just·er *also* **ad·jus·tor** \ə-ˈjəs-tər\ *n* (1673) : one that adjusts; *esp* : an insurance agent who investigates personal or property damage and makes estimates for effecting settlements

ad·just·ment \ə-ˈjəs(t)-mənt\ *n* (1644) **1** : the act or process of adjusting **2** : a settlement of a claim or debt in a case in which the amount involved is uncertain or in which full payment is not made **3** : the state of being adjusted **4** : a means (as a mechanism) by which things are adjusted one to another **5** : a correction or modification to reflect actual conditions — **ad·just·men·tal** \ə-ˌjəs(t)-ˈment-ᵊl, ˌaj-ˌəs(t)-\ *adj*

ad·ju·tan·cy \ˈaj-ət-ən-sē\ *n* (1775) : the office or rank of an adjutant

ad·ju·tant \ˈaj-ət-ənt\ *n* [L *adjutant-, adjutans*, prp. of *adjutare* to help — more at AID] (1600) **1** : a staff officer in the army, air force, or marine corps who assists the commanding officer and is responsible esp. for correspondence **2** : one who helps : ASSISTANT

adjutant general *n, pl* **adjutants general** (1645) **1** : the chief administrative officer of an army who is responsible esp. for the administration and preservation of personnel records **2** : the chief administrative officer of a major military unit (as a division or corps)

¹**ad·ju·vant** \ˈaj-ə-vənt\ *adj* [F or L; F, fr. L *adjuvant-, adjuvans*, prp. of *adjuvare* to aid — more at AID] (1574) : serving to aid or contribute : AUXILIARY

➔ ²**adjuvant** *n* (1609) : one that helps or facilitates; *as* **a** : an ingredient (as in a prescription or a solution) that modifies the action of the principal ingredient **b** : something (as a drug or method) that enhances the effectiveness of medical treatment

Ad·le·ri·an \ad-ˈlir-ē-ən, ad-\ *adj* [Alfred *Adler*] (1933) : of, relating to, or being a theory and technique of psychotherapy emphasizing the importance of feelings of inferiority, a will to power, and overcompensation in neurotic processes

¹**ad–lib** \ˈad-ˈlib\ *vb* **ad–libbed**; **ad–lib·bing** [*ad lib*] *vt* (1919) : to deliver spontaneously ~ *vi* : to improvise esp. lines or a speech — **ad–lib** *n*

²**ad–lib** *adj* (1935) : spoken, composed, or performed without preparation

ad lib *adv* [NL *ad libitum*] (ca. 1811) **1** : in accordance with one's wishes **2** : without restraint or limit

¹**ad li·bi·tum** \(ˈ)ad-ˈlib-ət-əm\ *adv* [NL, in accordance with desire] (1610) : AD LIB (rats fed *ad libitum*)

²**ad libitum** *adj* (1769) : omissible according to a performer's wishes — used as a direction in music; compare OBBLIGATO

ad·man \ˈad-ˌman\ *n* (1909) : one who writes, solicits, or places advertisements

ad·mass \ˈad-ˌmas\ *adj* [*advertising* + *mass*] *chiefly Brit* (1955) : of, relating to, or characteristic of a society that devotes itself chiefly to the production, promotion, and consumption of material goods

ad·mea·sure \ad-ˈmezh-ər, -ˈmā-zhər\ *vt* **-sured**; **-sur·ing** [ME *amesuren*, fr. MF *amesurer*, fr. *a-* (fr. L *ad-*) + *mesurer* to measure] (14c) : to determine the proper share of : APPORTION

ad·mea·sure·ment \-ˈmezh-ər-mənt, -ˈmā-zhər-\ *n* (1598) **1** : determination and apportionment of shares **2** : determination or comparison of dimensions **3** : DIMENSIONS, SIZE

Ad·me·tus \ad-ˈmēt-əs\ *n* [L, fr. Gk *Admētos*] : a king of Pherae who is saved by Apollo from his fated death when his wife Alcestis offers to die in his place

ad·min·is·ter \əd-ˈmin-ə-stər\ *vb* **ad·min·is·tered**; **ad·min·is·ter·ing** \-st(ə-)riŋ\ [ME *administren*, fr. MF *administrer*, fr. L *administrare*, fr. *ad-* + *ministrare* to serve, fr. *minister* servant — more at MINISTER] *vt* (14c) **1** : to manage or supervise the execution, use, or conduct of (~ a trust fund) **2 a** : to mete out : DISPENSE (~ punishment) **b** : to give ritually (~ the last rites) **c** : to give remedially (~ a dose of medicine) ~ *vi* **1** : to perform the office of administrator **2** : to furnish a benefit : MINISTER (~ to his ailing friend) **3** : to manage affairs *syn* see EXECUTE — **ad·min·is·tra·ble** \-strə-bəl\ *adj* — **ad·min·is·trant** \-strənt\ *n*

ad·min·is·trate \-ˌstrāt\ *vt* **-trat·ed**; **-trat·ing** [L *administratus*, pp. of *administrare*] (1631) : ADMINISTER

ad·min·is·tra·tion \əd-ˌmin-ə-ˈstrā-shən, (ˌ)ad-\ *n* (14c) **1** : the act or process of administering **2** : performance of executive duties : MANAGEMENT **3** : the execution of public affairs as distinguished from policy-making **4 a** : a body of persons who administer **b** *cap* : a group constituting the political executive in a presidential government **c** : a governmental agency or board **5** : the term of office of an administrative officer or body — **ad·min·is·tra·tion·al** \-shnəl, -shən-ᵊl\ *adj* — **ad·min·is·tra·tion·ist** \-sh(ə-)nəst\ *n*

ad·min·is·tra·tive \[illegible]\ *adj* (1731) : of or relating to administration or an administration : EXECUTIVE — **ad·min·is·tra·tive·ly** *adv*

administrative county *n* (1888) : a British local administrative unit often not coincident with an older county

administrative law *n* (ca. 1902) : law dealing with the establishment, duties, and powers of and available remedies against authorized agencies in the executive branch of the government

ad·min·is·tra·tor \[illegible]\ *n* (15c) **1** : a person legally vested with the right of administration of an estate **2 a** : one that administers esp. business, school, or governmental affairs **b** : a priest appointed to administer a diocese or parish temporarily

ad·min·is·tra·trix \[illegible]\ *n, pl* **-tra·tri·ces** \[illegible]\ [NL] (1626) : a woman administrator esp. of an estate

ad·mi·ra·ble \ˈad-m(ə-)rə-bəl\ *adj* (15c) **1** : deserving the highest esteem : EXCELLENT **2** *obs* : exciting wonder : SURPRISING — **ad·mi·ra·bil·i·ty** \ˌad-m(ə-)rə-ˈbil-ət-ē\ *n* — **ad·mi·ra·ble·ness** \ˈad-m(ə-)rə-bəl-nəs\ *n* — **ad·mi·ra·bly** \-blē\ *adv*

ad·mi·ral \ˈad-m(ə-)rəl\ *n* [ME, fr. MF *amiral* admiral & ML *admiralis* emir, *admiralius* admiral, fr. Ar *amīr al-* commander of the (as in *amīr al-baḥr* commander of the sea)] (15c) **1** *archaic* : the commander in chief of a navy **2 a** : FLAG OFFICER **b** : a commissioned officer in the navy or coast guard who ranks above a vice admiral and whose insignia is four stars — compare GENERAL **3** *archaic* : FLAGSHIP **4** : any of several brightly colored butterflies (family Nymphalidae)

admiral of the fleet (1660) : the highest-ranking officer of the British navy

ad·mi·ral·ty \ˈad-m(ə-)rəl-tē\ *n* (15c) **1** *cap* : the executive department or officers formerly having general authority over British naval affairs **2** : the court having jurisdiction of maritime questions; *also* : the system of law administered by admiralty courts

Admiralty mile *n* (ca. 1901) : NAUTICAL MILE a

ad·mi·ra·tion \ˌad-mə-ˈrā-shən\ *n* (15c) **1** *archaic* : WONDER **2** : an object of esteem **3 a** : a feeling of delighted or astonished approbation **b** : the act or process of regarding with admiration

ad·mire \əd-ˈmī(ə)r\ *vb* **ad·mired**; **ad·mir·ing** [MF *admirer*, fr. L *admirari*, fr. *ad-* + *mirari* to wonder — more at SMILE] (1590) *vt* **1** *archaic* : to marvel at **2** : to regard with admiration **3** : to think highly of often in a somewhat impersonal manner (~ a man's capacity for work) *syn* see REGARD — **ad·mir·er** *n* — **ad·mir·ing·ly** \-ˈmī-riŋ-lē\ *adv*

ad·mis·si·ble \əd-ˈmis-ə-bəl, ad-\ *adj* [F, fr. ML *admissibilis*, fr. L *admissus*, pp. of *admittere*] (1611) **1** : capable of being allowed or conceded : PERMISSIBLE (behavior that was hardly ~) **2** : capable or worthy of being admitted (foreign products ~ to a domestic market) — **ad·mis·si·bil·i·ty** \-ˌmis-ə-ˈbil-ət-ē\ *n*

ad·mis·sion \əd-ˈmish-ən, ad-\ *n* (15c) **1 a** : the act or process of admitting **b** : the state or privilege of being admitted **c** : a fee paid at or for admission **2 a** : the granting of an argument or position not fully proved **b** : acknowledgment that a fact or statement is true *syn* see ADMITTANCE — **ad·mis·sive** \-ˈmis-iv\ *adj*

ad·mit \əd-ˈmit, ad-\ *vb* **ad·mit·ted**; **ad·mit·ting** [ME *admitten*, fr. L *admittere*, fr. *ad-* + *mittere* to send] *vt* (15c) **1 a** : to allow scope for : PERMIT **b** : to concede as true or valid (compelled to ~ his failure) **2** : to allow entry (as to a place, fellowship, or privilege) (each ticket ~s two persons) (*admitted* to the university) ~ *vi* **1** : to give entrance or access **2 a** : ALLOW, PERMIT (this order ~s of two interpretations) **b** : to make acknowledgment — used with *to* *syn* see ACKNOWLEDGE — **ad·mit·ted·ly** \-ˈmit-əd-lē\ *adv*

ad·mit·tance \əd-ˈmit-ᵊn(t)s, ad-\ *n* (1590) **1** : permission to enter a place : ENTRANCE **2** : the reciprocal of the impedance of a circuit

syn ADMITTANCE, ADMISSION mean permitted entrance. ADMITTANCE is usu. applied to mere physical entrance to a locality or a building; ADMISSION applies to entrance or formal acceptance (as into a club) that carries with it rights, privileges, standing, or membership.

ad·mix \ad-ˈmiks\ *vt* [back-formation fr. obs. *admixt* mingled (with), fr. ME, fr. L *admixtus*] (15c) : MINGLE, BLEND

ad·mix·ture \ad-ˈmiks-chər\ *n* [L *admixtus*, pp. of *admiscere* to mix with, fr. *ad-* + *miscēre* to mix — more at MIX] (1605) **1 a** : the act of mixing **b** : the fact of being mixed **2 a** : something added by mixing **b** : a product of mixing : MIXTURE

ad·mon·ish \ad-ˈmän-ish\ *vt* [ME *admonesten*, fr. MF *admonester*, fr. (assumed) VL *admonestare*, alter. of L *admonere* to warn, fr. *ad-* + *monēre* to warn — more at MIND] (14c) **1 a** : to indicate duties or obligations to **b** : to express warning or disapproval to esp. in a gentle, earnest, or solicitous manner **2** : to give friendly earnest advice or encouragement to *syn* see REPROVE — **ad·mon·ish·er** *n* — **ad·mon·ish·ing·ly** \-ish-iŋ-lē\ *adv* — **ad·mon·ish·ment** \-mənt\ *n*

ad·mo·ni·tion \ˌad-mə-ˈnish-ən\ *n* [ME *amonicioun*, fr. MF *amonition*, fr. L *admonition-, admonitio*, fr. *admonitus*, pp. of *admonere*] (14c) **1** : gentle or friendly reproof **2** : counsel or warning against fault or oversight

ad·mon·i·to·ry \ad-ˈmän-ə-ˌtōr-ē, -ˌtȯr-\ *adj* (1594) : expressing admonition : WARNING — **ad·mon·i·to·ri·ly** \-ˌmän-ə-ˈtōr-ə-lē, -ˈtȯr-\ *adv*

ad·nate \ˈad-ˌnāt\ *adj* [L *adgnatus*, pp. of *adgnasci* to grow on, fr. *ad-* + *nasci* to be born — more at NATION] (1661) : grown to a usu. unlike part esp. along a margin (a calyx ~ to the ovary) — **ad·na·tion** \ad-ˈnā-shən\ *n*

ad nau·se·am \ad-ˈnȯ-zē-əm *also* -ˌam\ *adv* [L] (1647) : to a sickening degree

ad·nexa \ad-ˈnek-sə\ *n pl* [NL, fr. L *annexa*, neut. pl. of *annexus*, pp. of *annectere* to bind to — more at ANNEX] (1899) : conjoined, subordinate, or associated anatomic parts; *specif* : the temporary structures and esp. the embryonic membranes of the embryo — **ad·nex·al** \-səl\ *adj*

ado \ə-ˈdü\ *n* [ME, fr. *at do*, fr. *at* + *don*, *do* to do] (14c) **1** : fussy bustling excitement : TO-DO **2** : time-wasting bother over trivial details (wrote the paper without further ~) **3** : TROUBLE, DIFFICULTY

\ə\ abut \ᵊ\ kitten, F table \ər\ further \a\ ash \ā\ ace \ä\ cot, cart \au̇\ out \ch\ chin \e\ bet \ē\ easy \g\ go \i\ hit \ī\ ice \j\ job \ŋ\ sing \ō\ go \ȯ\ law \ȯi\ boy \th\ thin \t͟h\ the \ü\ loot \u̇\ foot \y\ yet \zh\ vision [illegible] see Guide to Pronunciation